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Roentgen Therapy for Infections: An Historical Review

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Radiation was used extensively for the treatment of all types of infections before the advent of antibiotics. Although this mode of therapy is now in disrepute, radiation therapists of that era were firm believers in the ability of radiation to cure infections. A review of the literature suggests, but certainly does not prove, that low-dose local radiation, in the range of 75 to 300 roentgens, is an effective treatment modality for a wide variety of infections. Two then-prevailing rationales held that the effect was due either to radiation damage to the immune cells, causing stimulation of the immune response, or to the increase in local inflammation with resultant increased blood flow. Modern research has been limited but provides support for both arguments.

Although there are no present indications for using radiation as therapy for infectious disease, a reasonable argument can be made from the available data that radiation is effective for the treatment of localized infections. The mechanisms of low-dose radiation as a treatment for infections remain unclear. The known and probable long-term sequelae of low-dose local irradiation preclude its common use for this condition. Nevertheless, it is hoped that this review will stimulate investigations into this relatively unexplored area of radiobiology.

INTRODUCTION

Ionizing radiation was used for nearly 50 years for the treatment of all types of infectious disease. Radiation was commonly used at the Hospital of the University of Pennsylvania, and this experience has been reviewed previously [1]. Personal experience of one of the authors (PJH) emphasized the apparent usefulness of roentgen therapy for many types of infections, particularly post-operative parotitis and erysipelas. Other studies showed the apparent ability of radiation to alter the natural history of gas gangrene [2], acute otitis media [3], peritonitis [4], pneumonia [5], encephalitis [6], herpes simplex [7], and a myriad of other infections [1].

Well into the age of antibiotics, radiation was given emergently to leukemic children and adults with perianal abscesses [D'Angio G: oral communication, March 1990]. Some leukemic children also developed lesions of the skin and buccal mucosa. D'Angio and colleagues reported in 1959 that, "[t]he children bite on these and ulceration and infection follow swiftly, with large, foul, deep craters resulting frequently. Roentgen therapy has been found to be of considerable assistance in the control of these local lesions" [8].

The recent review by Order and Donaldson on the use of radiation therapy in benign diseases briefly discusses the modern viewpoint on radiation for infectious disease [9]. The authors randomly distributed a questionnaire to radiation therapists

Abbreviation: PMN: polymorphonuclear (cell) asking if they would or would not treat infectious disease. They report that 97 percent would not treat fungal infections, 99 percent would not treat tuberculosis, 97 percent would not treat viral infections, 96 percent would not treat bacterial infections, 99 percent would not treat leprosy, and 73 percent would not treat warts.

The standard of care before the advent of chemotherapy for infections differed from the present reluctance to use radiation. For example, in 1941, in the Radiation Therapy Section at Walter Reed General Hospital, 82.5 percent of their patients were treated for benign lesions, which had decreased to 60 percent by 1945 [10]. A review of radiation therapy treatments given by Dr. John L. Barner, at Lawson General Hospital in Atlanta from 1941 to 1946, showed that 50 percent or more of his treatments were for benign diseases, of which 50 percent were for acute or chronic infections, including fungal infections, viral infections, furunculosis, parotitis, and otitis media [10]; however, these years marked the end of the era for roentgen treatment of infections. Antibiotics were being introduced, rendering roentgen therapy for infections mostly obsolete. By 1946, it was difficult, if not impossible, to get studies on the treatment of infections by radiation published [Hodes PJ: personal recollection] because radiation had been completely supplanted by antibiotics.

The present proscription of radiation for infectious disease, as shown by the Order and Donaldson survey, is no doubt based mainly on the well-known tumorigenic effects of radiation. It may, however, also be based partly on the belief by modern radiation therapists that radiation for infections was ineffective. Although a better therapy, antibiotics, supplanted radiation as a treatment modality, this does not in itself negate the possible efficacy of radiation in infectious diseases. To try to determine if the use of radiation to speed recovery from infectious disease was valid, we review herein reports and studies of radiation treatment of infectious disease. These treatments were primarily performed in the first half of the century. Particular attention is paid to clinical studies which include a control population and to well-designed experimental studies. Unfortunately, that literature does not have many papers which meet today's criteria for acceptability. From what is available, we have chosen papers which thoroughly document their materials and methods and provide some sort of numerical analysis of their results. We have made no attempt to cover completely the published literature on the use of radiation, as the vast majority of the publications were anecdotal and non-scientific by modern standards. We believe the studies selected suggest the possibility that ionizing radiation was a successful treatment for infectious disease. Furthermore, we believe that the use of radiation in this context still presents an interesting challenge to radiobiology.

GAS GANGRENE

Gas gangrene in the pre-antibiotic era was a frequent complication of traumatic injury and an infrequent complication of operations and injections. The disease had a mortality of approximately 50 percent with standard surgical treatment of thorough debridement and early amputation [11,12]. Otherwise, treatment options were few. One, introduced in the 1930s, was radiation therapy of the afflicted area; J.F. Kelly was its principal proponent. Radiation therapy attracted enough attention that the U.S. Army's World War II vintage Picker portable field radiographic unit was designed to give field radiation therapy to treat open wounds prophylactically against gas gangrene [12].

Kelly collected and, in 1938, reported case histories from his and others' experiences [13]. He found that, of 105 non-diabetic patients treated locally for limb gangrene with doses of 100 roentgens twice a day for two or three days, six (5.7 percent) had died. Of 18 truncal gangrene cases, four (22 percent) had died, two of whom had received insufficient treatment. Furthermore, the need for amputation had been reduced from the 100 percent standard in some hospitals to a 4 percent death rate with radiation and no amputation. These results were superior to the historical results of 50 percent survival without early amputation. In the absence of randomized studies, however, it is difficult to know if the better survival was due to radiation or to better patient selection, misdiagnosis, or possibly the use of less radical surgical procedure.

Several experimental studies were done in attempts to prove the usefulness of radiation in the treatment of gas gangrene. Kelly reported that guinea pigs injected with *Clostridium welchii* died in spite of being treated with roentgen therapy (reported in [1]). Erb and Hodes injected *Clostridium welchii* into pigeons as a model for gas gangrene; they found that radiation and sulfonamides were of no value, whereas serum treatment was beneficial (reported in [1]). Dowdy and Sewell developed a dog model for gas gangrene [14]; they found an apparent but statistically insignificant improvement in survival for dogs treated with 100 roentgens once or twice a day (for an unspecified time) after being infected. The time to death of the non-surviving dogs was doubled (24 days to 45 days) by treatment.

Thus there are several clinical series from the pre-antibiotic era that suggest low doses of radiation appear to be markedly effective in preventing and curing gas gangrene. There is also experimental support of this system in a dog model. This research culminated in the plan to use radiation therapy in the field during World War II for the prophylaxis of wounds, although there are no reports of this procedure ever being put into practice. Radiation for gas gangrene has apparently not been practiced in the post-antibiotic era.

PERITONITIS

J.F. Kelly, buoyed by his results with radiation against the anaerobic gas gangrene bacteria, collected case reports on the use of radiation for acute peritonitis [4]. He compared the results of treatment of appendicitis complicated by acute peritonitis by four means; *(1)* general measures only; *(2)* sulfonamide and general measures; *(3)* sulfonamides, X-rays, and general measures; and *(4)* X-rays and general measures. His radiation dosages were not fixed and ranged from 50 to 75 roentgens per fraction and one to three fractions per day for several days. He found a 65 percent (71/109) mortality for general measures only, a 38 percent (16/42) mortality for antibiotics, a 33 percent (7/21) mortality for antibiotics and radiation, and a 20 percent (6/30) mortality for X-rays along (p for X-rays, versus general measures only, $<.01$). The experience in the literature aside from Kelly's is scant. It is therefore difficult to reach a firm conclusion on the efficacy of radiation for peritonitis.

OTITIS MEDIA

Several papers reported on using local roentgen therapy for the treatment of otitis media. The two largest studies were a collection of case histories by Lucinian [15] and a case-control study by Dowdy and colleagues [3]. Dowdy and co-workers randomly chose 27 cases of purulent otitis media (as diagnosed by examination) for

TABLE 1
Radiation Therapy for Acute Otitis Media
(Adapted from [3])

Type	Number	Duration after Treatment (days)	Total Duration (days)
Catarrhal[a]	15	6.5	8.6
Purulent (no radiation therapy)	18	22.1	27.2
Purulent (with radiation therapy)[b]	11	17.6	21.2

[a]Fourteen received one treatment, one received two treatments of 100 roentgens.
[b]Eight received one treatment, three received two treatments of 100 roentgens.

conventional therapy (myringotomy) and 15 cases of purulent otitis media for treatment by myringotomy and 100 roentgens either once or twice, 24 hours apart, using a field encompassing the ear, mastoid, and posterior nasopharynx. Fifteen cases of catarrhal otitis media (no purulence noted) were also treated with roentgen therapy (100 roentgens once or twice). Their results are reproduced in Table 1. As can be seen, the duration of disease of purulent otitis media without complications was reduced by roentgen rays from 27.2 days to 21.2 days (a 25 percent reduction). The duration of the disease with complications (advanced mastoiditis) was reduced from 61.0 days to 45.0 days; however, the range of disease duration was not given, and so statistical manipulations cannot be performed. Clinically, they noted that the duration of the discharge from the purulent disease was reduced after radiation and that the discharge became more watery after treatment. Although there were no control cases included in this study to allow comparison of the courses of the treated and untreated catarrhal disease, there was immediate relief of pain noted after the radiation treatment and no progression to purulent disease.

Lucinian's paper includes a control series of patients chosen from the records of another physician. The selection criteria were not given. He found that pain was relieved consistently after the first treatment, followed by a gradual reduction in fever over ten to 15 days and a reduction and thinning of the discharge. He also states that radiation obviated tympanic membrane perforation if it had not occurred before radiation therapy was begun.

In this disease, the results may not have been the direct action of radiation on the disease but rather an indirect action moderated through the ability of radiation to shrink lymphoid tissues. This process would open an obstructed eustachian tube and allow drainage, thus aiding in the resolution of the infection, much as tympanostomy tubes are used in modern medicine. A similar technique of placing a small radium applicator in the posterior nasopharynx at an obstructed eustachian tube to open the tube was used well into the modern era. Loeb reviewed the literature and presented his 30-year follow-up on this technique in 1979 [16]. He characterized his responses as good, fair, or poor. In all, he treated 28 patients, of whom 24 had good responses and two had fair responses. He had no second malignancies in this small group. Hardy and Bordley reported, in 1954, on a controlled, randomized trial in which half of the candidates with chronic serous otitis media and hearing loss were irradiated with local radium implants and half were not [17]. At five years' follow-up, the treated patients had smaller adenoid masses and better hearing than the controls. No statistics were given.

Thus the role of radiation in the treatment of otitis media may be more easily understood than in other infectious diseases. Its success appears to arise from the ability of radiation to reopen eustachian tubes blocked by swollen lymphoid tissue, allowing drainage and resolution to occur. It is also of interest to note that, in Loeb's review of the literature, there were no local second malignancies in over 3,000 patients with 15 to 30 years' follow-up.

CARBUNCLES AND FURUNCLES

A carbuncle is a deep-seated loculated abscess with interconnecting sinuses. Sepsis can arise from untreated carbuncles. A furuncle is a more isolated infection, arising in a sweat gland or a hair follicle. Complicated furuncles of the upper lip were reported to have a pre-antibiotic mortality of 50 percent [18]. Radiation was accepted as a positive intervention in both diseases, although firm data were lacking. In 1933, Baensch reported the results of 206 patients with facial furuncles, half of whom received radiation [19]. The irradiated patients had a mortality of 2 percent versus 10 percent for untreated patients ($p < 0.02$). Pendergrass and Hodes stated their impression, but no quantitative analysis was performed, that the duration of infection in acute furunculosis was shortened in 71 of 79 (90 percent) of their patients with head and neck furunculosis, and their chronic cases showed a 50 percent decrease in disease length [1]. Because they had no untreated controls, no definitive conclusions could be reached. A smaller study of 20 cases of carbunculosis by Pendergrass and Hodes showed rapid improvement in 45 percent of the cases, moderate improvement in 30 percent, and little to no improvement in 25 percent [1].

Carp in 1927 [20] published a comparison of radiation, surgery, conservative treatments (poultices, carbolization, narcotics, cold compresses, Dakin compresses), ichthyol (ammonium bituminosulfonate), "Thermolite" ice bags and antiseptics, or circuminjection of blood [21]. The cases were not randomly assigned to the treatments, and the selection criteria for various treatments were not given. Twenty-two non-diabetic cases were treated with radiation, receiving two-thirds to three-fourths of a skin erythema dose (probably 350–400 roentgens). Twelve responded successfully, nine, all on the back of the neck, required operations, and one, with an upper lip lesion, died. Carp lists several cases of extensive necrosis, but he does not give details as to whether these were secondary to the abscesses or the radiation. These results can be compared with 56 cases which received surgery alone; 54 of these cases were successfully resolved, although four required re-operations, and two died. Carp notes that radiation did little to relieve pain, but radiation resolved the lesion more quickly than did surgery.

Newell gives a brief description of a double-blind study on the effect of radiation on carbuncle resolution [22]. He treated every patient presenting with a carbuncle with radiation, but, in alternate cases, a lead block was placed by the technician in front of the beam to prevent exposure of the lesion to the radiation. He treated with 100 roentgens daily for three successive days. No difference in the time to resolution was noted; however, when he treated patients with 300 roentgens in one sitting, he noted occasional "miraculous" resolutions of the carbuncles with treatment. These data were given in the discussion of another paper. A search of the literature does not reveal the promised follow-up article.

Soto and colleagues studied an animal model of subcutaneous infections [23]. They injected *E. coli* into sites on the upper and lower backs of rabbits and then irradiated the lower back, allowing comparison of the rate of healing of the two lesions in the same animal. They used 600 roentgens for all experiments. Irradiation 24 hours before injections or within five hours after injection decreased the reaction to the bacteria and hastened the resolution of the lesion. Irradiation 24 hours or seven days after injection did not affect the outcome. When either a mildly virulent or a highly virulent strain of *Staphylococcus aureus* was used, there was no benefit noted from irradiation immediately after the injections. To study the effect of radiation on inflammation, 600 roentgens were given in the same experimental design 24 hours before or immediately after injection of croton oil. A reduction in inflammation was found when radiation was given.

The use of radiation for the treatment of localized infections appears to have continued in isolated areas into the modern era. Barker and Gould of the Dermatology Department of the General Infirmary of Leeds, England, reported in 1979 on the use of radiation combined with antibiotics for two cases of furunculosis of the face. In both cases the infections resolved without complications. They mention only incidentally that radiation was part of the treatment, implying that this measure was a common practice [24]. A second paper out of the General Infirmary of Leeds by Fairris, Jones, Mack, and Rowell in 1984 discusses a double-blinded, controlled trial of radiation for the treatment of palmoplantar pustulosis [25]. They state that radiation was then often being used for the treatment of this condition. They treated nine paired sites on three patients, with one site receiving 100 rads every 21 days for three treatments, and the other site receiving placebo treatments. They found that radiation did not resolve the condition better than the placebo treatment in eight of nine pairs.

Thus radiation for local infections has a mixed pedigree in the literature. Early, uncontrolled studies and a few animal studies appear to indicate it is effective; however, two small controlled studies show it to be unsuccessful.

PNEUMONIA

Rousseau et al. summarized the case reports of the use of radiation for acute pneumonia. They also added their observations in the treatment of sulfonamide-resistant pneumococcal pneumonia [5]. Their patients had failed several day trials of sulfonamide antimicrobials and were taken off the antimicrobials before treatment. The patients received 200 roentgens every 36 hours for one to three doses. They reported that, of 104 patients treated, only six died (5.7 percent), which was below their community pneumonia death rate of 28 percent.

Several attempts were made experimentally to confirm the benefit of radiation on the resolution of acute pneumonias. Fried showed, using guinea pigs, that artificially induced pneumonia treated with 90–95 roentgens decreased the degree of lung hepatization [26]. Hodes and Lieberman studied the effect of radiation on pneumonia in dogs (reported in [1]). Type I and Type III pneumococci were instilled into 50 dogs to produce pneumonias. The sicker animals were given radiation; 160 to 200 roentgens were delivered daily for two to four days. All control animals died in about two days. Six of 14 treated animals survived ($p < .01$), and the average duration of survival of the animals that died was about nine days.

There are no modern studies on the use of radiation for pneumonia because antibiotics have eliminated the need for this treatment modality. It appears, however, from the limited clinical trials and animal experiments that radiation may have had some activity against bacterial pneumonia.

RELATED EXPERIMENTAL STUDIES

Radiation therapy was in its infancy when the first experiments were performed on its use for treating infectious disease. Williams, in his classic 1901 textbook, briefly describes four sets of experiments on the ability of X-rays to alter the course of infections [27]. Reider inoculated virulent staphylococci into mice, rabbits, and guinea pigs and then irradiated the animals. The X-rays had no effect. When Reider injected the animals with tubercle bacilli and then irradiated them, however, the course of the disease was delayed, although all of the animals eventually died. During the same year, Kratzenstein, while discussing Müsham's work, presented the results on 26 guinea pigs injected with tuberculosis and confirmed that X-rays could inhibit the rate of progression of systemic tuberculosis but not cure it. Lortet and Genoud injected the ground spleen of a very tubercular guinea pig and injected it into eight healthy guinea pigs. Two days later, they began irradiating the injection site of three of the guinea pigs, an hour a day for two months. The treated guinea pigs remained without disease, whereas the untreated guinea pigs developed ulcers at the injection site and inguinal lymphadenopathy. Finally, Fiorentine and Linachi are reported by Williams to have injected a culture of the tubercle bacilli into the peritonea of guinea pigs and then irradiated their abdomens. The irradiated animals showed fewer nodules than did the injected but unirradiated animals. They also report that, in another series of experiments, the X-rays prevented any nodule formation in the irradiated region.

A particularly well-done study showing the curative ability of radiation was by Goldberg and colleagues [28]. They intranasally injected St. Louis encephalitis virus into mice. Then the mice were given one-fourth human erythema doses of X-rays (probably equivalent to 130–140 roentgens) daily for up to 12 treatments or death. On this regimen, 50 percent (19/38) of the treated mice survived, whereas 2 percent (1/53) of the control mice survived ($p < .01$). The activity of low-dose total-body irradiation against systemic viral disease was then independently discovered over 50 years later by Shen and colleagues, using the Friend virus in mice [29,30]. These workers found 150 centigray given on days 5 and 12 after inoculation cured 35 of 35 mice, whereas 35 of 35 mice not irradiated died within 40 days of inoculation, with a median survival of 32 days. Ten mice irradiated only ten days after inoculation all died, but the median time to death extended to 50 days, and, similarly, mice treated on days 12 and 18 had only two of ten mice survive, with a median survival of 62 days. They postulate that the mechanism of survival was that the selective radiolethality of these doses of radiation to T-suppressor cells allowed the expression of an otherwise inhibited immune response to the virus.

Other, more modern studies were done by Kahn. He hypothesized that irradiation, by an "anti-localizing effect," increased the dissemination of both biomolecules and bacteria from an injection site. His first experiment studied the result of local irradiation of rabbits on the prevention of diphtheria by anti-diphtheria toxin [31]. The antitoxin was injected into a field which had been irradiated with 1,000 roentgens. Simultaneously with the antitoxin, he injected a lethal amount of diphtheria toxin into an unirradiated site. He found a significantly increased level of protection from the antitoxin when it was injected into a site irradiated 24 hours previous to the injection ($p < .01$), and an apparent though statistically insignificant (at the 0.05 level) protection when injection occurred at one to three hours after and at seven days after irradiation [31]. Similar experiments using lesser radiation dosages 24 hours before inoculation showed a decreasing protection with decreasing dose of radiation, with no, minimal, and good protection at 100, 150, and 300 rads, respectively [32]. He also found that locally irradiating the flank of rabbits with 1,000 rads and then injecting a high dose of staphylococci subcutaneously at that site led to the death of all the irradiated rabbits and none of the control animals [33]. This result, he concluded, was again due to the ability of low-dose radiation to prevent the normal localizing response of the body to foreign antigens.

THEORIES OF THE EFFECT OF ROENTGEN RAYS ON INFECTIONS

There were two main theories in the 1930s of how radiation aided the resolution of infections. Neither theory proposed the direct action of radiation on bacteria because bactericidal doses are in the range of 100,000 roentgens. Desjardins theorized that the effect of radiation was due to leukocytolysis [34]. He held that the leukocytes (lymphocytes and polymorphonuclear cells [PMNs]) are extremely sensitive to low doses of radiation. During inflammation, PMNs are the first and most abundant cell type. As the reaction proceeds, the area is infiltrated by mononuclear macrophages. If the inflammation is not resolved in a few days, there will be an increased population of lymphocytes. According to Desjardins, radiation in the doses used for infections will cause the leukocytes to disintegrate, releasing the bacterolytic compounds they contain. Furthermore, the radiation or the products of radiation induce an increase in the phagocytic strength of the macrophages and PMNs, which further aids the resolution of the infection and the inflammatory process. Modern experiments dispute the radiosensitivity of PMNs [35,36]. A recent study does show increased death of PMNs if they are stressed after irradiation [37].

The second major theory was that of Pendergrass and Hodes [1]. They held that the doses of radiation used are too small to induce much damage in the cellular components of inflammation. Rather, they felt that the effect of radiation is to induce local dilation of the blood vessels [38], much like a very active poultice. This induction of active hyperemia, similar to that described by Altemeier and Jones [39] for irradiated abdominal and peritoneal tissues, increases the rate and quantity of blood flow through the irradiated area. The inflammatory response itself is a potent inducer of hyperemia, and so radiation may be able to add little to the active area of inflammation; however, the area surrounding the active response will be converted from passive hyperemia into active hyperemia by radiation. The increased blood flow, they held, increases the temperature and flow of electrolytes to the site of inflammation and increases the lymphatic runoff, all of which increases the efficiency of the anti-infective and anti-inflammatory response. Kahn's work supports this latter theory.

Modern theories of the effects of radiation supply little advance over these theories. It has been known from many studies that whole-body irradiation induces an increase in the phagocytic activity of the macrophages [40,41], and activated macrophages are much more radioresistant than are resting macrophages [42]. There is also a variation in the radiation sensitivity of B cells and T cells [43]. Moreover, Cheers and Waller found that lethally (900 r) and sublethally total-body irradiated (700 r) mice had an increased resistance to inoculation with *Brucella* *abortus* [40]. These studies seem to agree with the basic theory of Desjardins that a change in the cellular response to infection by radiation is possible. A study by Steel and co-workers showed that whole-body irradiation induced increased concentrations of inflammatory proteins and eicosanoids in the peritonea of mice [44]. This process would lead to increased inflammation in surrounding tissues and changes in local blood flow, as predicted by Pendergrass and Hodes.

CONCLUSIONS

It is possible, then that, through indirect mechanisms, radiation may alter the ability of the body to respond to infections. The exact nature of these mechanisms is still unclear. Although modern radiobiology has centered on the direct effects of radiation, such as DNA damage [45], the role of indirect effects in the response of tissue to radiation is still being actively studied. For example, Denekamp has revitalized interest in the role of destruction of tumor vasculature in the control of tumors [46]. The theorized role of the immune system for the control of cancer is also enjoying regained popularity [47]. There are presently clinical trials under way to test the therapeutic abilities of lymphokines such as tumor necrosis factor and interferon, modern names for the old lymphotoxins, for the treatment of cancer [48].

Of course, none of this research warrants a return to the use of radiation for the treatment of infections. The incidence of second malignancies after the treatment of benign diseases has been well documented [49]. Nonetheless, the possible ability of low-dose radiation to modify the course of infectious diseases is an interesting phenomenon in itself and may be worth experimental testing. Should it prove to be efficacious, it could open the door to new insights into the interactions of radiation and the body in the treatment of cancer.

REFERENCES

1. Pendergrass E, Hodes P: Roentgen irradiation in the treatment of inflammations. Amer J Roent 45:74–106, 1941
2. Kelly JF, Dowell DA: Twelve-year review of X-ray therapy of gas gangrene. Radiology 37:421–439, 1941
3. Dowdy AH, Heatly CA, Pierce WW: The evaluation of roentgen irradiation as an adjunct of the treatment of acute otitis media. Radiolgy 32:661–668, 1939
4. Kelly JF: The X-ray treatment of acute peritonitis. Radiology 38:299–306, 1942
5. Rousseau JP, Johnson WM, Harrell GT: The value of roentgen therapy in pneumonia which fails to respond to the sulfonamides. Radiology 38:281–289, 1942
6. Portmann UV, Lough R: Roentgen therapy for acute encephalitis. Amer J Roent 53:597–602, 1945
7. Hall WC: Radiation treatment of herpes simplex. Amer J Roent 39:393–396, 1938
8. D'Angio GJ: Roentgen therapy of certain complications of acute leukemia in childhood. Amer J Roent 82:541–553, 1959
9. Order SE, Donaldson SS: Radiation Therapy of Benign Diseases. Berlin, Springer-Verlag, 1990, p 212
10. Friedman M: Radiation therapy. In Radiology in World War II. Edited by AL Ahnfeldt. Washington, DC, Department of the Army, 1966, p 207
11. Eliason EL, Erb WH, Gilbert PD: The Clostridium welchii and associated organisms. Surg Gyn Obst 64:1005–1014, 1937
12. de Lorimer AE: Equiment and supply. In Radiation in World War II. Edited by AL Ahnfeldt. Washington, DC, Department of the Army, 1966, p 67
13. Kelly JF, Dowell DA, Russum C, Colein FE: The practical and experimental aspects of roentgen treatment of bacillus welchii (gas gangrene) and other gas-forming infections. Radiology 31:608–619, 1938
14. Dowdy AH, Sewell RL: Roentgen radiation in experimental Clostridium welchii infection (gas gangrene) in dogs: Preliminary report. Radiology 37:440–442, 1941

15. Lucinian JH: Treatment of otitis media and mastoiditis by the roentgen ray. Amer J Roent 36:946–953, 1936
16. Loeb WJ: Radiation therapy of the nasopharynx: A 30 year review. Laryngoscope 89:16–21, 1979
17. Hardy WG, Bordley JE: Controlled study on the effect of nasopharyngeal irradiation on a group of school age children. Ann Otol Rhinol Laryngol 63:816–826, 1954
18. Meakins JD: The Practice of Medicine. St. Louis, MO, CV Mosby, 1936
19. Baensch W: Zur röntgentherapie des gesichtsfurunkels. Strahlentherapie 447:188, 1933
20. Carp L: Treatment of carbuncles, a comparison of four different methods. Ann Surg 86:702–706, 1927
21. Carp L: Circuminjection of autogenous blood in the treatment of carbuncles. Arch Surg 14:868–890, 1927
22. Newell RR: Discussion. Radiology 32:314, 1939
23. Soto JA, Brunschwig A, Schultz FW: An experimental study of the effects of X-radiation upon acute pyogenic infection of the skin and subcutaneous tissues. Surgery 3:393–600, 1938
24. Barker DJ, Gould DJ: A pustular eruption in the chin (a variant of pyoderma faciale?). Acta Dermatovener 58:549–550, 1979
25. Fairris GM, Jones DH, Mack DP, Rowell NR: Superifical X-ray therapy in the treatment of palmoplantar pustulosis. Br J Dermatol 111:499–500, 1984
26. Fried C: Die artifizielle pneumonie und ihre bestrahlung. Strahlentherapie 58:430, 1937
27. Williams FH: The Roentgen Rays in Medicine and Surgery as an Aid in Diagnosis and a Therapeutic Agent. New York, The MacMillan Company, 1901
28. Goldberg SA, Brodie M, Stanley P: Effect of X-ray on experimental encephalitis in mice inoculated with the St. Louis strain. Proc Soc Exp Biol Med 32:587–590, 1935
29. Shen R-N, Hoenbeck NB, Lu L, Young P, Brahmi Z, Broxmeyer HE: Curative effect of split low dosage total-body irradiation on mice infected with the polycythemia-inducing strain of the Friend virus complex. Cancer Res 48:2399–2403, 1988
30. Shen R-N, Hornback NB, Lu L, Chen LT, Brahmi Z, Broxmeyer HE: Low dose total body irradiation: A potent anti-viral agent in vivo. Int J Rad Oncol Biol Phys 16:165–170, 1989
31. Kahn RL, Kim SH, Curtis AC, Simons CS: X irradiation and toxin neutralization by antitoxin. J Inf Dis 107:325–331, 1960
32. Kahn RL, Botzler RG, Miller NS: Antilocalization following minimal focal X-irradiation. Rad Res 30:634–639, 1967
33. Kahn RL: Irradiation and tissue immunity II. Response to injection of staphylococci in X-irradiated skin areas of rabbits. J Inf Dis 110:107–113, 1962
34. Desjardins AU: The action of roentgen rays on inflammatory conditions. Radiology 38:274–280, 1942
35. Button LN, DeWolf WC, Newburger PE, Jacobson MS, Levy SV: The effecs of irradiation on blood components. Transfusion 21:419–425, 1981
36. Valerius NH, Johansen KS, Nielsen OS, Platz P, Rosenkvist J, Sørensen H: Effect of in vitro X-irradiation of lymphocyte and granulocyte function. Scand J Haematol 27:9–18, 1981
37. Bueschler ES, Gallin JI: Effects of storage and radiation on human neutrophil function in vitro. Inflammation 11:401–416, 1987
38. Pendergrass EP, Hodes PJ, Griffith JQ: Effect of roentgen rays on the minute vessels of the skin in man. Amer J Roent 52:123–127, 1944
39. Altemeier WA, Jones HC: Experimental peritonitis: Its prevention by roentgen irradiation. JAMA 114:27–29, 1940
40. Cheers C, Waller R: Activated macrophages in congenitally athymic 'nude' mice and lethally irradiated mice. J Immunol 115:844–847, 1975
41. Westman A: Studies on the influence of the roentgen and radium rays on phagocytosis. Acta Radiologica 2:57–69, 1923
42. den Otter W, Evans A, Alexander P: Differentiation of immunologically specific cytotoxic macrophages into two types on the basis of radiosensitivity. Transplantation 18:421–428, 1974
43. Riggs JE, Lussier AM, Lee S-K, Appel MC, Woodland RT: Differential sensitivity among B cell subpopulations. J Immunol 141:1799–1807, 1988
44. Steel LK, Hughes HN, Walden TL Jr: Quantitative, functional and biochemical alterations of the peritoneal cells of mice exposed to whole body gamma-irradiation. I. Int J Rad Oncol Biol Phys 53:943–964, 1988
45. Suit HD, Urano M: Radiation biology for radiation therapy. In Clinical Radiation Oncology. Edited by CC Wang. Littleton, MA, PSG Publishing, 1988, pp 17–55

46. Denekamp J: Induced vascular collapse in tumors: A way of increasing therapeutic gain in cancer therapy. In BIR Report 19: The Scientific Basis of Modern Radiotherapy. Edited by NJ McNally. London, UK, British Institute of Radiology, 1989, pp 63–70
47. Kreuger GRF: Abnormal variation of the immune system as related to a cancer. In Influence of the Host on Tumor Development. Edited by RB Herberman. Dordrecht, The Netherlands, Kluwer Academic Publishers, 1989, pp 139–161
48. Rosenberg SA, Packard BS, Aebersold PM, et al: Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma: A preliminary report. N Engl J Med 319:1678–1688, 1988
49. Goldschmidt H, Gorson RO, Lassen M: Dermatologic radiotherapy and thyroid cancer. Arch Dermatol 119:383–390, 1983